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(54) Title: ANTI-CTLA-4 ANTIBODY AND CPG-MOTIF-CONTAINING SYNTHETIC OLIGODEOXYNUCLEOTIDE COMBINATION THERAPY FOR CANCER TREATMENT

(57) Abstract: The invention relates to administration of an anti-CTLA-4 antibody, particularly human antibodies to human CTLA-4, such as those having amino acid sequences of antibodies 3.1.1, 4.1.1, 4.8.1, 4.10.2, 4.13.1, 4.14.3, 6.1.1, 11.2.1, 11.6.1, 11.7.1, 12.3.1.1, 12.9.1.1, and MDX-010, in combination with an immunostimulatory nucleotide, *i.e*, CpG ODN PF3512676, for treatment of cancer. The invention relates to administering a combination of an anti-CTLA-4 antibody and CpG ODN PF3512676 as neoadjuvant, adjuvant, first-line, second-line, and third-line therapy of cancer, whether localized or metastasized, and at any point(s) along the disease continuum (*e.g*, at any stage of the cancer).

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Although the individual use of anti-CTLA-4 antibodies or ODNs to induce an anti-tumor response hold great promise in the treatment of cancer, there remains a need to develop novel therapies to treat tumors, more particularly, solid tumors, with such immunotherapeutic approaches.

Summary of the Invention

Development of new therapeutic regimens, particularly those capable of augmenting or potentiating the anti-tumor activity of the immune system of the patient, while reducing the cytotoxic side effects of current chemotherapeutics, is necessary. The present invention provides such regimens.

Thus, in one embodiment, the invention provides a method for the treatment of cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of an anti-CTLA-4 antibody, or antigen-binding portion thereof, in combination with a therapeutically effective amount of CpG ODN PF3512676 (CpG 7909 (also known as ProMune); TCG TCG TTT TGT CGT TTT GTC GTT; SEQ ID NO:37). In one embodiment, the method is a non-vaccine method.

In one embodiment, said the CpG ODN is administered daily, every other day, twice a week, or weekly.

In one embodiment, said treatment is a therapy selected from the group consisting of neoadjuvant therapy, adjuvant therapy, first-line therapy, second-line therapy, and third-line therapy.

Depending on the embodiment, said cancer is selected from the group consisting of brain cancer, breast cancer, cervical cancer, colorectal carcinoma, cutaneous T-cell lymphoma, gastric cancer, head and neck cancer, liver cancer, lung cancer, melanoma, acute myeloid leukemia, Non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, and sarcoma.

In other embodiments, said therapeutically effective amount of said human anti-CTLA-4 antibody ranges from about 0.1 mg/kg to 50 mg/kg, or from about 0.3 mg/kg to 20 mg/kg, including but not limited to a therapeutically effective amount of said human anti-CTLA-4 antibody selected from the group consisting of at least 1 mg/kg, at least 3 mg/kg, at least 6 mg/kg, at least 10 mg/kg, and at least 15 mg/kg.

In one embodiment, said anti-CTLA-4 antibody, or antigen-binding portion thereof, is at least one antibody selected from the group consisting of (a) a human antibody having a binding affinity for CTLA-4 of about 10^{-8} or greater, and which inhibits binding between CTLA-4 and B7-1, and binding between CTLA-4 and B7-2; (b) a human antibody having an amino acid sequence comprising at least one human CDR sequence that corresponds to a CDR sequence from an antibody selected from the group consisting of 4.1.1, 4.8.1, 4.10.2, 4.13.1, 4.14.3, 6.1.1, 11.2.1, 11.6.1, 11.7.1., 12.3.1.1, 12.9.1.1, and 10D1; (c) a human antibody having the amino acid sequence of a heavy and/or light chain of an antibody selected from the group consisting of 4.1.1, 4.8.1, 4.10.2, 4.13.1, 4.14.3, 6.1.1, 11.2.1, 11.6.1, 11.7.1., 12.3.1.1, 12.9.1.1, and 10D1; (d) an antibody, or antigen-binding portion thereof, that competes for binding with CTLA-4 with at least one antibody having the amino acid